II. REMARKS

Formal Matters

Claims 1 and 3-27 are pending after entry of the amendments set forth herein.

Claims 1-4 and 21 were examined and were rejected. Claims 5-20 were withdrawn from consideration.

The specification is amended. Support for the amendments to paragraph 0049 is found at, e.g., paragraphs 00169 and 00179. As such, no new matter is added by the amendments to paragraph 0049.

Claims 1, 3, and 21 are amended. The amendments to claims 1, 3, and 21 were made solely in the interest of expediting prosecution, and are not to be construed as acquiescence to any objection or rejection of any claim. The claim dependency of claim 3 is amended; as such, no new matter is added. Support for the amendments to claims 1 and 21 is found in the claims as originally filed, and throughout the specification, in particular at the following exemplary locations: claim 1: paragraphs 0042, 0043, 0047, 0049, 00169, and 00179; and claim 21: paragraphs 0047, 0049, 00169, and 00179. Accordingly, no new matter is added by these amendments.

Claim 2 is canceled without prejudice to renewal, without intent to acquiesce to any rejection, and without intent to surrender any subject matter encompassed by the canceled claim. Applicants expressly reserve the right to pursue any canceled subject matter in one or more continuation and/or divisional applications.

Claims 22-27 are added. Support for new claims 22-27 is found in the claims as originally filed, and throughout the specification, including the following exemplary locations: claim 22: Example 1, paragraph 00168; paragraph 0039; and paragraph 0045; claim 23: Example 1, paragraph 00168; paragraph 0039; and paragraph 0045; claim 24: paragraphs 0042 and 00163; and claims 25-27: paragraphs 0049, 00169, and 00179. Accordingly, no new matter is added by these new claims.

Applicants respectfully request reconsideration of the application in view of the remarks made herein.

Examiner Interview

The undersigned Applicants' representative thanks Examiner Jon Weber and Examiner Kailash Srivastava for the courtesy of a telephonic interview which took place on February 26, 2007, and which was attended by Examiners Weber and Srivastava, inventor Karl Weisgraber, and Applicants' representative Paula A. Borden.

During the interview, the rejections under 35 U.S.C. §102(b) and §112, first and second paragraphs, were discussed. The amendments to the claims reflect the discussions which took place during the interview.

Rejection under 35 U.S.C.§112, first paragraph

Claims 1-4 and 21 were rejected under 35 U.S.C. §112, first paragraph, as allegedly failing to comply with the written description requirement. Claim 1-4 and 21 were rejected under 35 U.S.C.§112, first paragraph, as allegedly lacking enablement.

Claims 1-4 and 21; written description

The Office Action stated that "only a full-length apoE and one 22 kDa N-terminal fragment are disclosed." Office Action, page 5. Applicants respectfully traverse the rejection.

The instant specification provides adequate written description.

The instant specification states that isolated stable folding intermediates of apolipoprotein E (apoE) are provided; and that the isolated stable folding intermediates are useful for identifying compounds that alter the structure and/or activity of such stable folding intermediates. Specification, paragraph 0038.

The instant specification states that isolated apoE stable folding intermediates have one or more of the following characteristics:

1) a molten globule structure;
2) near native-like structural features;
3) a significant amount of native secondary structure, structural compactness, and internal mobility with exposure of its hydrophobic core; and
4) enhanced ability to bind lipid.

Specification, paragraph 0040. Working examples of isolated stable folding intermediates that exhibit one or more of these characteristics were provided. Specification, Example 1, paragraphs 00163-00179. See, e.g., paragraphs 00170-00179.

The instant specification states that apoE stable folding intermediates are formed *in vitro* under conditions of low pH and denaturation, and provides a list of suitable denaturing agents, as well as examples of suitable conditions for forming an apoE stable folding intermediate. Specification, paragraphs 0041, 0042, 0049, and 00108.

The instant specification states that the source of apoE for use in preparing isolated apoE stable

folding intermediates can be any of various well-known apoE polypeptides, including apoE fragments. Specification, paragraphs 0043-0046.

The instant specification describes how to determine whether a given condition or set of conditions gives rise to an apoE stable folding intermediate. Specification, paragraph 0048.

The instant specification provides working examples of apoE stable folding intermediates. Specification, Example 1, paragraphs 00163-00179. Example 1 describes isolated stable folding intermediates of the N-terminal 22-kDa fragments of both apoE3 and apoE4. The specification states that the 22-kDa fragments of both apoE3 and apoE4 formed stable folding intermediates. Specification, paragraphs 00168 and 00169; and Figures 2A and 2B.

Given the extensive description in the specification, as noted above, those skilled in the art would recognize that Applicants had possession of the instant invention as claimed.

Claims 1-4 and 21; enablement

The Office Action stated that the specification does not reasonably provide enablement for a composition comprising any apoE intermediate or the 22 kDa N-terminal fragment thereof, or an isolated apoE4 stable folding intermediate. Applicants respectfully traverse the rejection.

Applicants note that the Office Action stated that the specification is enabling for a full-length apoE stable folding intermediate.

The instant specification provides ample enabling disclosure.

The instant specification describes characteristics of apoE stable folding intermediates.

As noted above, the instant specification describes characteristics of isolated apoE stable folding intermediates; and states that isolated apoE stable folding intermediates have one or more of the following characteristics:

1) a molten globule structure;
2) near native-like structural features;
3) a significant amount of native secondary structure, structural compactness, and internal mobility with exposure of its hydrophobic core; and
4) enhanced ability to bind lipid.

Specification, paragraph 0040. Working examples of isolated stable folding intermediates that

exhibit one or more of these characteristics were provided. Specification, Example 1, paragraphs 00163-00179. See, e.g., paragraphs 00170-00179.

The instant specification describes how to make an apoE stable folding intermediate.

The instant specification states that apoE stable folding intermediates are formed *in vitro* under conditions of low pH and denaturation, and provides a list of suitable denaturing agents, as well as examples of suitable conditions for forming an apoE stable folding intermediate. Specification, paragraphs 0041, 0042, 0049, and 00108. The instant specification describes how to determine whether a given condition or set of conditions gives rise to an apoE stable folding intermediate. Specification, paragraph 0048.

Amino acid sequences of a variety of apoE polypeptides, including apoE fragments, were known in the art.

The instant specification states that the source of apoE for use in preparing isolated apoE stable folding intermediates can be any of various well-known apoE polypeptides, including apoE fragments. Specification, paragraphs 0043-0046. As noted in paragraph 0043, the amino acid sequences of a variety of apoE polypeptides were known in the art. Furthermore, apoE fragments, e.g., a 22 kDa N-terminal fragment, of apoE were known in the art. See, e.g., paragraph 0046, citing Morrow et al. ((2000) *Biochem.* 39:11657-11666).

The instant specification provides working examples of at least two different apoE stable folding intermediates.

The instant specification provides working examples of apoE stable folding intermediates. Specification, Example 1, paragraphs 00163-00179. Example 1 describes isolated stable folding intermediates of the N-terminal 22-kDa fragments of both apoE3 and apoE4. The specification states that the 22-kDa fragments of both apoE3 and apoE4 formed stable folding intermediates. Specification, paragraphs 00168 and 00169; and Figures 2A and 2B.

In view of the extensive teachings in the specification, including working examples, regarding how to make apoE stable folding intermediates, those skilled in the art could readily make apoE stable folding intermediates as claimed, without undue experimentation.

Conclusion as to the rejections under 35 U.S.C.§112, first paragraph

Applicants submit that the rejections of the claims discussed above under 35 U.S.C.§112, first paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejections.

Rejection under 35 U.S.C.§112, second paragraph

Claims 1-4 and 21 were rejected under 35 U.S.C. §112, second paragraph, as allegedly indefinite.

Claim 1

The Office Action stated that the phrase "isolated apoE stable folding intermediate" renders claim 1 unclear, vague, and indefinite. The Office Action stated that it is not clear how without knowing the length or amino acid composition or amino acid sequence, the intermediate apoE will stably fold and what conditions the intermediate will fold. Applicants respectfully traverse the rejection.

There is no requirement that the amino acid sequence of an apoE polypeptide be known in order to form a stable folding intermediate. Furthermore, as noted above, the instant specification provides ample description of the conditions for formation of an apoE stable folding intermediate. As such, claim 1 is clear.

Claims 2-4

The Office Action stated that claims 2-4 are unclear, vague, and indefinite because there is no mention of the amino acid composition or amino acid length comprising the apoE4 stable folding intermediate. The Office Action stated that appropriate parameters/properties of the apoE4 stable folding intermediate are required to clearly appraise the apoE4 stable folding intermediate. Applicants respectfully traverse the rejection.

As noted above, there is no requirement that the amino acid sequence of an apoE polypeptide be known in order to form a stable folding intermediate. Furthermore, as noted above, the conditions for generating an apoE stable folding intermediate are amply described in the specification. Also as noted above, the specification provides a working example of a stable folding intermediate of a 22 kDa N-terminal fragment of apoE4. As explained by Dr. Weisgraber during the telephone interview, a full-length apoE4 polypeptide would form a stable folding intermediate under conditions such as those used to form a stable folding intermediate of a 22 kDa N-terminal fragment of apoE4. As such, claims 2-4 are clear.

Conclusion as to the rejections under 35 U.S.C.§112, second paragraph

Applicants submit that the rejections of claims 1-4 and 21 under 35 U.S.C.§112, second paragraph, have been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

Rejection under 35 U.S.C.§102(b)

Claims 1-4 and 21 were rejected under 35 U.S.C.§102(b) as allegedly anticipated by Morrow et al. ((2000) *Biochem.* 39:11657-11666; "Morrow").

The Office Action stated that Morrow discloses a composition comprising isolated human apoE stable folding intermediate. Applicants respectfully traverse the rejection.

Morrow discusses compositions at various concentrations of guanidine HCl or urea, at pH 7.4. As explained during the telephone interview, Morrow does not disclose an isolated human apoE stable folding intermediate, where the stable folding intermediate is at least about 80% pure, and where the stable folding intermediate is formed at a pH of from about 1.0 to about 5.0. As such, Morrow cannot anticipate claim 1 as amended, or any claim depending directly or indirectly from claim 1.

Conclusion as to the rejection under 35 U.S.C.§102(b)

Applicants submit that the rejection of claims 1-4 and 21 rejected under 35 U.S.C. §102(b) has been adequately addressed in view of the remarks set forth above. The Examiner is thus respectfully requested to withdraw the rejection.

III. CONCLUSION

Applicants submit that all of the claims are in condition for allowance, which action is requested. If the Examiner finds that a telephone conference would expedite the prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

The Commissioner is hereby authorized to charge any underpayment of fees associated with this communication, including any necessary fees for extensions of time, or credit any overpayment to Deposit Account No. 50-0815, order number UCAL-282.

Respectfully submitted,
BOZICEVIC, FIELD & FRANCIS LLP

Date: Mar. 2, 2007

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